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Full Papers

Modeling-Based Approach towards On-Scale Implementation of a Methanethiol-Emitting Reaction

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Abstract:

Utilizing kinetic process modeling, the conditions for a pharmaceutical guanylation reaction were optimized to promote controlled generation of methanethiol and efficient removal from the off-gas stream via wet scrubbing. Optimization of the kinetic model identified two guanylation reaction temperature profiles that reduced the maximum off-gas flow rate by approximately 75% while increasing the reaction cycle time by only 15−23%. The identified reaction conditions were quickly verified in laboratory-scale experiments and implemented in the scale-up of this process from kilo laboratory to pilot plant scale. Additionally, computational fluid dynamics calculations of the sodium hypochlorite and sodium hydroxide wet scrubber were used to demonstrate that methanethiol oxidation within the wet scrubber was rapid. Within this system, methanethiol bubbles were only expected to travel approximately 40 mm before being completely oxidized. Upon scale-up, the process-modeling-based approach described here provided methanethiol removal efficiencies of greater than 99.9999% for methanethiol inlet concentrations between 10 and 60 wt % using standard pilot plant equipment.

1. Introduction

Reactions emitting volatile organic compounds (VOC) pose unique environmental challenges that must be addressed upon scale-up. The generation of certain VOCs, such as sulfur analogs, adds the specific challenge of odor control. Sulfur analog compounds are generated as byproducts in a variety of reactions commonly used in the chemical and pharmaceutical industries. Dimethyl sulfide is generated as a byproduct during the oxidation of alcohols by DMSO, such as in the Swern oxidation,[1] and when performing sulfur ylid chemistry.[2] The decomposition of hemithiol acetals in acidic conditions could also lead to the generation of trace amounts of methanethiol. Efficient implementation of such processes requires thorough understanding of the VOC generation rate as well as knowledge of the ultimate fate of the VOC.

In the production process of a pharmaceutical intermediate, a guanylation reaction was developed in which 1 mol equiv of methanethiol (MeSH) was generated as a byproduct. Methanethiol is a highly flammable gas that causes irritation to the skin and eyes and is toxic by inhalation. It is commonly recognized by its strong disagreeable odor at thresholds as low as 1.6 ppb. As a result, control of methanethiol emissions needed to be addressed upon scale-up of this reaction. The objective of this work was to scale-up the guanylation reaction utilizing standard pharmaceutical pilot plant equipment while reducing MeSH emissions to below the odor detection threshold.

Without any downstream treatment of the MeSH off-gas produced during a single batch on scale-up, 2.52×10^9 m^3 of air would be required to dilute the MeSH concentration to below the odor threshold. Thus, the scale-up of this reaction required the use of a treatment method yielding extremely high removal efficiencies. Techniques for the treatment of thiol compounds are commonly found in the literature. Thiol compounds can be adsorbed into granular porous materials made out of activated carbon or zeolite.[3,4] However, physical adsorption is reversible and the adsorbed VOC may be displaced by subsequent adsorption of heavier vapors. Catalytic incineration of VOCs is one of the most cost-effective treatment options. The presence of methanethiol, however, may cause deactivation of the Pt catalyst that is commonly used in catalytic incineration processes, thus reducing their efficiency.[5] Another widespread method for controlling thiol emissions is adsorption within an aqueous-alkaline solution via wet scrubbing.[6] This technique relies on the equilibrium solubility of these compounds in the alkaline solutions, which can limit the thiol concentration of the gas stream to be treated. The removal efficiency of wet scrubbers can be enhanced with the use of oxidizing agents. Chemical oxidation via wet scrubbers enables the economical

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treatment of large quantities of gas.[7] Oxidation reactions of thiol compounds are irreversible and generally occur in short timescales. These properties can be exploited to increase the efficiency of the wet scrubber. A number of oxidizing agents, such as sodium hypochlorite, oxygen, hydrogen peroxide and chlorine dioxide, can be used to remove sulfur compounds. Sodium hypochlorite is the most widely used oxidizing agent for chemical scrubbing. It is relatively inexpensive and has a high oxidation potential with most sulfur compounds.[8]

The work presented here highlights the use of process modeling and simulation tools to identify optimal process conditions for the safe and efficient scale-up of the guanylation reaction to a 45-kg pharmaceutical pilot plant scale. Additionally, the use of a sparged, stirred tank as a wet scrubber for methanethiol treatment is described. The wet scrubber used chemical oxidation as the treatment method and employed sodium hypochlorite as the oxidizing agent.

2. Experimental Section

2.1. Methanethiol Detection: Scrubber Efficiency Measurements. Because of low limits of detection, ease of use, and relative specificity, Draeger-Tubes were used throughout the scale-up of the guanylation reaction to detect methanethiol. Specific Draeger-Tubes used were Mercaptan 0.1/a (0.1–2.5 ppm), Mercaptan 0.5/a (0.5–5 ppm), and Mercaptan 20/a (20–100 ppm). Measurements from laboratory-scale reactors and wet scrubbers were taken via direct insertion of the Draeger-Tube into the vessel head space. Samples from kilo laboratory and pilot plant systems were first collected into evacuated sample chambers. The sample chambers were then connected to the inlet side of the Draeger-Tubes for analysis.

In addition to detection by Draeger-Tube, methanethiol emissions from laboratory and kilo laboratory guanylation reactions were monitored via online mass spectrometry. Emissions from the head space of both the reactor and subsequent wet scrubbers were followed with an Ametek/Dycor explosion proof, multiport quadrupole mass spectrometer (ProMaxion model).

Calibration of the mass spectrometer signal was accomplished via sensitivity factors and correction to a known nitrogen carrier gas flow rate following the procedure from Hettenbach et al.[9] Mass spectrometer calibration gases were obtained from Airgas (20 ppm of methanethiol in nitrogen and 1500 ppm of methanethiol in nitrogen). The sensitivity factor for methanethiol relative to nitrogen was calculated from the 1500 ppm calibration gas and determined to be 0.5. The mass spectrometry signal for methanethiol contains two roughly equal peaks at $m/z = 47$ and $m/z = 48$. During the MeSH measurements the sum of these peaks was divided by the nitrogen signal at $m/z = 28$. This ratio was then multiplied by the sensitivity factor and the known nitrogen flow rate to estimate the MeSH content of the sample stream. Although the mass spectrometer was able to detect methanethiol at the 1500 ppm concentration, detection of methanethiol below 20 ppm was not possible. As a result, the mass spectrometer was only capable of detecting methanethiol in the head space of the guanylation reactor and not in the head space of the wet scrubber(s). On the basis of this detection limit, the use of the mass spectrometer was discontinued prior to the pilot plant scale-up.

***Scheme 1.* Scrubber reactions: methanethiol oxidation by sodium hypochlorite and sodium hydroxide**[a]

$$1.0\ CH_3SH + 3.0\ NaOCl + 1.0\ NaOH \longrightarrow 1.0\ CH_3SO_3Na + 3.0\ NaCl + 1.0\ H_2O$$

[a] NaOH maintains an alkaline pH within the scrubber and provides a rapid initial deprotonation of MeSH via acid–base chemistry. NaOCl is the oxidizing agent, with 3 mol equiv required for the full oxidation of methanethiol. Note: The concentration of the sodium chloride byproduct in the scrubber solution was <0.4 mol/L at the end of the guanylation reaction. The effect of the sodium chloride formation on the MeSH solubility in the scrubber solution was negligible and not considered in the models described here.

2.2. Generalized Methanethiol Wet Scrubbing System. The wet scrubber utilized throughout the scale-up of the guanylation reaction consisted of a sparged, stirred tank containing an aqueous sodium hypochlorite and sodium hydroxide solution. The gas stream to be treated was fed to the scrubber vessel via a subsurface addition line or dip pipe. The oxidation of methanethiol within this system is shown in Scheme 1. Although complete oxidation of methanethiol with only NaOCl is possible, NaOH was utilized to maintain an alkaline pH within the scrubber (methanesulfonic acid is produced via oxidation of MeSH). The following design criteria were employed to minimize the risk of a MeSH release during the guanylation reaction:

1 The scrubber contained a minimum of 6 mol equiv of NaOCl and 2 mol equiv of NaOH per mole of methanethiol gas expected.

2 To prevent leaks from the process train, the entire system was operated under a slight negative pressure via application of vacuum on the down stream end of the wet scrubber(s). The reaction vessel was set to reflux, and 5 °C cooling fluid was applied on the overhead condenser to prevent solvent evaporation into the scrubber.

3 A nitrogen sweep of the guanylation reactor head space was implemented to direct MeSH vapor towards the scrubber(s) and to maintain an inert environment within the system.

4 The expected total gas flow rate (MeSH and N_2 sweep) was evaluated and ensured to be below the allowable maximum gas flow rate based on equipment vent sizes.

5 A dry trap was included between the reactor and scrubber vessels to eliminate the possibility of back flow of the scrubbing solution into the guanylation reaction.

3. Modeling Section

3.1. Kinetic Modeling of the Guanylation Reaction. Kinetic modeling of the guanylation reaction was performed with DynoChem version 3.2 from PFD Inc. The

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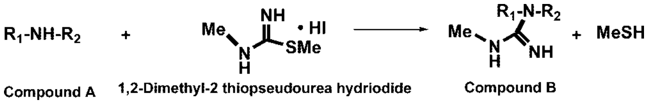
Scheme 2. **Guanylation reaction: methanethiol is formed as compound A is guanylated by 1,2-dimethyl-2-thiopseudoureahydriodide**



DynoChem software employs a mechanistic approach for reaction modeling and simulation of unit operations. DynoChem also offers a platform to fit unknown or experimentally inaccessible parameters from experimental or measured plant data. The guanylation reaction is shown in Scheme 2. The thiol functional group acts as a leaving group as compound A is guanylated by 1,2-dimethyl-2-thiopseudoureahydriodide (thiourea), resulting in the formation of methanethiol. The off-gas curve obtained from the head space of the reactor shows that the methanethiol generation follows first-order reaction rate kinetics with respect to compound A (Figure 1). From the balanced chemical equation and the off-gassing trend, the following rate expression was proposed:

$$R_{\mathrm{B}} = R_{\mathrm{MeSH}} = k[\mathrm{A}][\mathrm{thiourea}]$$

where the reaction is assumed to be second-order overall and first-order with respect to both compound A and thiourea.

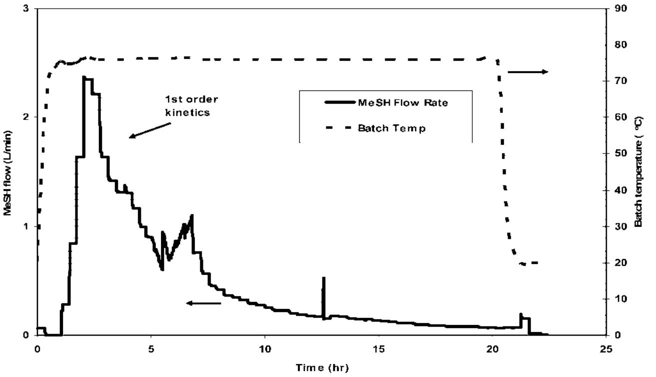


Figure 1. **Mass spectroscopy methanethiol measurements from the kilo laboratory batch. The off-gas curve obtained from the head space of the reactor shows that the methanethiol generation follows first-order reaction rate kinetics with respect to compound A. While the MS unit could detect MeSH in the head space of the reactor, the signals obtained from the head space of the first and second scrubbers were at the background level. Note: The increase in the apparent MeSH flow rate between 5 and 7 h was due to an increase in the nitrogen carrier gas flow rate during this time. This spike in the MS signal is most likely related to the equilibration of the methanethiol concentration throughout the reactor head space and dry trap void volumes.**

The guanylation reaction is a multiphase system. This system contains one bulk liquid phase (solvent), two solid phases (one for compound A and another for thiourea), and a gas phase (MeSH being evolved). The reaction was assumed to take place in the bulk liquid phase. The kinetic model needed to account for the phase transfer of compound A and thiourea from the solid phases to the liquid phase and for the phase transfer of MeSH from the bulk liquid phase to the gas phase. For the solid–liquid phase equilibrium, the mass transfer rate is estimated from the thermodynamic driving force. This is expressed by the following equation:

$$\frac{\mathrm{d}N_{\mathrm{A}}}{\mathrm{d}t} = k_{\mathrm{L}}A\left(C_{\mathrm{A}}^{*} - C_{\mathrm{A}}\right)$$

where N_A is the mass flux of the solute in the bulk liquid phase, k_LA is the solute mass transfer coefficient in the bulk liquid phase, C_A^* is the liquid-phase equilibrium solubility, and C_A is the bulk liquid concentration. The mass transfer coefficient is represented by the lumped parameter k_LA, which combines the overall transfer coefficient and the specific interfacial area. Experimental data showed that the bulk liquid-phase concentrations for compound A and thiourea are close to the equilibrium solubility for each component. This suggests that the mass transfer rate for both components is fast in comparison to the reaction rate. A high k_LA value for both solid phases (1 s^{-1}) was used in the DynoChem model to account for the high mass transfer rates. The equilibrium solubility for each solid phase was estimated using the van't Hoff equation:

$$C^{*} = A \exp(-B/RT)$$

where R is the gas constant (8.314 J mol^{-1} K^{-1}), T is the solution temperature (K), and A and B were fitted from laboratory experimental data. For the gas–liquid phase equilibrium, the mass transfer was also estimated from the thermodynamic driving force. The liquid-phase solubility of MeSH was modeled with Henry's law ($H_P = p_A/C^*$). The value of Henry's law constant was assumed to be that of MeSH in water (11500 Pa m^3/mol) since experimental data showed that MeSH had low solubility in the bulk liquid phase, similar to its behavior in water. Laboratory mass spectroscopy results showed that the rate of MeSH off-gassing was similar to the guanylation reaction rate, suggesting fast mass transfer from the liquid phase to the gas phase. From these results, the k_LA value for the gas–liquid phase transfer was set at 1 s^{-1} and was assumed to remain constant throughout the reaction.

HPLC data was collected for the guanylation reaction at 60 and 75 °C. From this data, the rate constant was determined to be 4.00×10^{-4} L mol/s (at 75 °C). The activation energy of the reaction, E_a, was determined by using the modified Arrhenius equation:

$$k = k_{\mathrm{ref}} \exp(-E_a/R[1/T - 1/T_{\mathrm{ref}}])$$

where k is the rate constant and k_{ref} is the rate constant at a reference temperature T_{ref}. The activation energy for the guanylation reaction was found to be 94 kJ/mol. Once these parameters were determined, DynoChem was used to predict reaction progress at the examined laboratory conditions. Figure 2 shows the kinetic model fit versus the experimental reaction

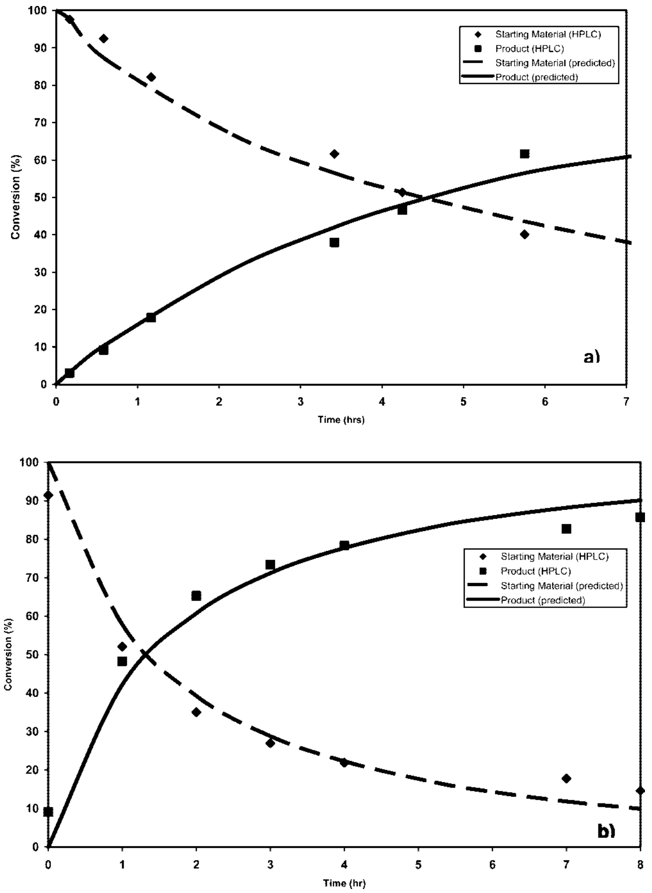


Figure 2. **Experimental data versus model-predicted profiles for the guanylation reaction at (a) 60 and (b) 75 °C. The model prediction is in close agreement with the HPLC data at 60 and 75 °C. The model-predicted and experimental curves represent the total concentration of the starting material (compound A) and the product (compound B).**

data. The model prediction was in close agreement with the HPLC data of compound A and compound B at both 60 and 75 °C. Additionally, once the kinetic model parameters were obtained, the accuracy of the model was tested by comparing the model prediction to the results previously obtained in the kilo laboratory. The MeSH model results were in close agreement with the kilo laboratory mass spectroscopy data (Figure 3).

3.2. Energy Balance Modeling of the Wet Scrubber. Online monitoring of methanethiol generation during the pilot plant implementation was performed via an energy balance around the wet scrubbing vessel. The wet scrubber was modeled via DynoChem as having an energy input term associated with the exothermic oxidation of the incoming methanethiol stream and an energy removal term via active jacket cooling of the vessel. The rate of reaction for methanethiol oxidation was assumed to be similar to the rate of oxidation of ethanethiol by chlorine dioxide (4.0×10^6 L/mol s) and taken from the literature.[13] The MeSH oxidation reaction was assumed to be instantaneous as compared to the time scale for energy removal via jacket cooling. Using data from a water solvent trial batch, the overall heat transfer coefficient for the wet scrubber vessel was calculated to be 894 W/K. The heat capacity of the scrubbing solution was assumed to be that of pure water, 4.2 kJ/mol K. The heat of reaction for the MeSH oxidation was determined from the data collected during the scrubber efficiency test (see section 4.3). The total heat removed from the vessel was divided by the amount of MeSH fed to the scrubber to give a heat of reaction of −1232 kJ/mol. The mass of the scrubbing solution was assumed to be constant throughout the guanylation reaction. Given this data and the jacket and batch temperature profiles, the methanethiol flow rate to the wet scrubber was calculated from the energy balance around the scrubber:

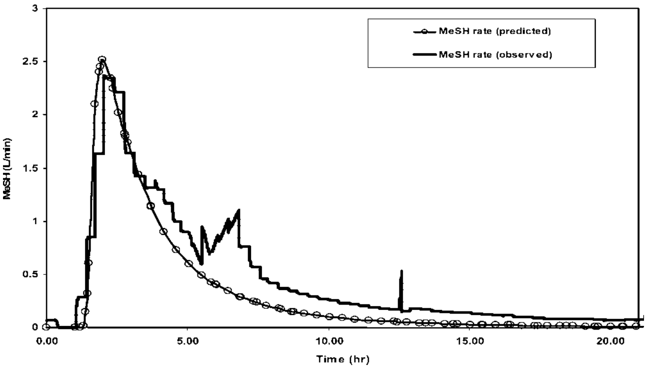


Figure 3. **Spectroscopy data versus model-predicted MeSH profiles for kilo laboratory batch. The predicted profile was corrected to reflect the sampling frequency of the mass spectrometer unit (approximately 50 min between sampling periods). The MeSH model results are in close agreement with the mass spectroscopy data.**

$$m_s Cp_s \frac{dT_s}{dt} = UA(T_s - T_j) + \Delta H_{rxn} F_{MeSH}$$

where m_s is the mass of the scrubber solution, Cp_s is the heat capacity of the scrubbing solution, T_s is the temperature of the scrubbing solution, UA is the overall heat transfer coefficient for the scrubber vessel, T_j is the temperature of the vessel jacket, ΔH_{rxn} is the heat released from the exothermic MeSH oxidation reaction, and F_{MeSH} is the flow rate of MeSH into the scrubber.

3.3. Computational Fluid Dynamics Simulations of the Wet Scrubber. CFD simulations were performed with the finite element software Comsol to evaluate the distance individual MeSH bubbles would travel inside the scrubber solution before being oxidized. Simple gas hold-up calculations could provide the residence time of a MeSH-containing bubble in the scrubber solution in the absence of a chemical reaction. However, this type of calculation does not provide details on the mass transport within the gas and liquid phases and ignores the effects of the oxidation reaction on the MeSH concentration within the bubble. In order to capture these factors a CFD-based approach was used.

The modeled system accounted for the convective and diffusive mass transport in both the gas and liquid phases and the oxidation reaction of the MeSH in the liquid phase. A schematic of the model is shown in Figure 4. As a worst-case scenario, the bubbles were modeled as rising at their terminal

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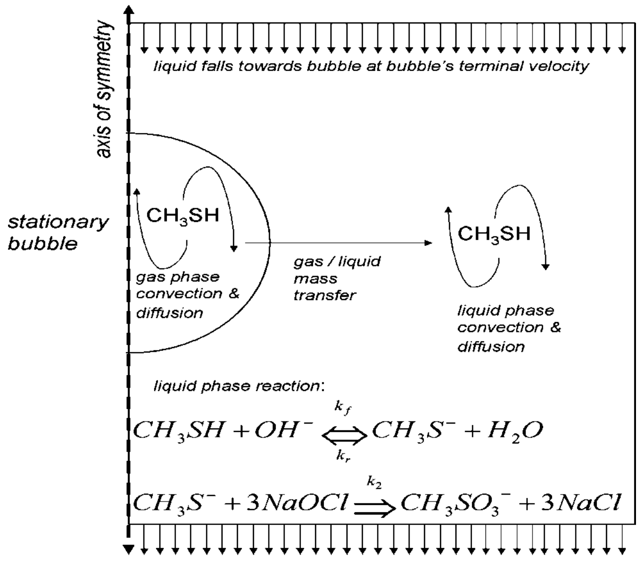

Figure 4. **CFD simulation of bubble rise distance. Simulations were performed to evaluate the distance a MeSH bubble would travel inside the scrubber solution. The modeled system accounted for the mass transport in the gas and liquid phases and for the MeSH oxidation reaction in the liquid phase. The bubbles were modeled as rising at their terminal velocity in a stagnant liquid. The reaction was modeled as a two-step process. The first step is an acid–base reaction to form (CH_3S^-). In the second step, CH_3S^- reacts with NaOCl.**

velocity in a stagnant liquid. In the actual stirred tank reactor, the mixing would be much better and would lead to not only higher mass transfer from the bubbles but also higher residence times for the bubbles. These higher bubble residence times would arise as the bubbles move around in the reactor with the fluid flow rather than straight up towards the top of the reactor as in the worst-case scenario. The bubbles would, therefore, be scrubbed to higher degrees of efficiency in the stirred tank reactor as compared to the worst-case scenario. The terminal velocities of the bubbles were found as a function of bubble size from the work of Leifer et al.[11] and Nguyen et al.[12]

The bubbles were modeled as two-dimensional half-circles in a rectangular box with a symmetry boundary condition at the axis spanning the length of the box. The control volume was defined to be twice as wide and four times as long as the bubble diameter. The fluid flow was solved first, followed by the mass transport and the reaction. The fluid flow was solved using the incompressible Navier–Stokes equations with fluid inside the bubble modeled as nitrogen and the bulk fluid modeled as water. In order to simplify the calculations, the bubble did not rise against the stagnant fluid; instead, the fluid fell towards the bubble at the bubble's terminal velocity. Thus, the boundary condition for the fluid inlet to the control volume was the fluid moving down towards the bubble at the bubble's terminal velocity. The boundary of the bubble was assumed to have slip symmetry, the control volume boundary opposite the axis of symmetry was assumed to be neutral, and the outlet of the control volume was set to vacuum.

Within the Comsol reaction engineering module, the oxidation reaction was modeled, and the results were then exported to the simulation where the fluid flow had been solved as a new convection and diffusion problem. The reaction was modeled as a two-step process, the first being an acid–base reaction where methanethiol (MeSH) reacts with sodium hydroxide (NaOH) to form (CH_3S^-). In the second step, CH_3S^- reacts with NaOCl. Step one, the acid–base reaction, was approximated as a reversible reaction with the ratio of the forward (k_f) and reverse (k_r) rate constants given by K_{eq}, where K_{eq} was determined from the pK_b for methanethiol. The rate constant for the second step was assumed to be the same as that for ethanethiol at pH 8.[13] The MeSH diffusion coefficients were set to 1×10^{-5} m^2/s in the gas phase and to 1×10^{-9} m^2/s in the liquid phase. The gas inside the bubble was composed of a 1:1 mixture of methanethiol and nitrogen. The bulk solution was composed of 0.6 N NaOH and 10% wt/wt NaOCl in water. The concentration of the species at the top of the control volume was assumed to be equal to the initial concentrations. The bottom surface of the control volume was set to the convective flux. The edge of the box opposite the axis of symmetry was assumed to be insulated. Methanethiol was allowed to diffuse into the liquid from the gas phase while all remaining species were retained in the liquid phase. This was achieved by setting the diffusivity in the gas phase for the other species to zero.

4. Results And Discussion

4.1. Kilo Laboratory Implementation of the Guanylation Reaction. The guanylation reaction was initially scaled-up to the kilo laboratory (4.5 kg) using the wet scrubber system shown in Figure 5. Methanethiol off-gas generated in the guanylation reaction was processed through three wet scrubbers in series before being released to the atmosphere. The first two scrubbers each contained NaOCl and NaOH. The third scrubber contained NaOH only. Aside from the third scrubber, the remainder of the equipment train was operated under a negative gauge pressure. Dry traps were provided between the reactor and first scrubber and between the first scrubber and second scrubber. Online mass spectroscopy measurements for MeSH levels were taken from the vapor streams exiting the reactor, the first scrubber, and the second scrubber. Additionally, discrete samples were taken of the MeSH concentration in the vapor phase exiting the first scrubber and the third scrubber via Draeger-Tubes. The guanylation reaction was run in the kilo laboratory by directly heating the reaction mixture to 75 °C and aging for 20 h at these conditions. Methanethiol was easily detected in the head space of the reactor via mass spectrometry (Figure 1). However, the MeSH signals observed in the head space of the first and second scrubbers were at the background level. As a result, an accurate determination of the scrubber efficiency based on MS data alone was not possible. Calculations based on discrete Draeger-Tube measurements were able to provide individual scrubber efficiencies of 99.99−99.9999%.

4.2. Modeling of Methanethiol off-Gassing Rates. Although the initial implementation of the guanylation reaction within the kilo laboratory was successful, a thorough understanding of the MeSH generation rate was necessary prior to further scale-up as such knowledge would provide the basis of the design for the wet scrubber system. The kilo laboratory mass spectroscopy data showed that the majority of the MeSH was emitted during the first 2−3 h of the guanylation reaction. While this might seem like a desirable property of the reaction, it

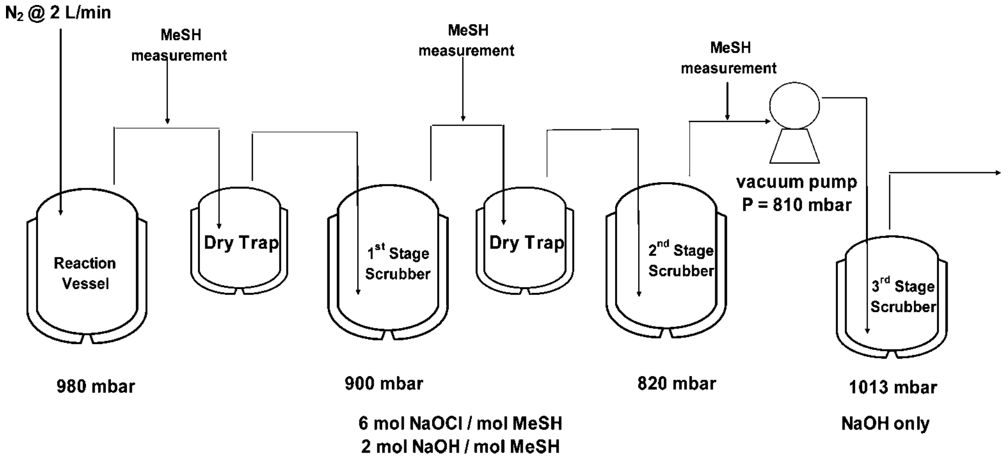

Figure 5. **Kilo laboratory scrubber setup. Methanethiol gas generated in the reaction vessel was processed through three wet scrubbers in series before being released to the atmosphere. The first two scrubbers each contained 6 mol of NaOCl and 2 mol of NaOH per mole MeSH expected. The third scrubber contained NaOH only. The equipment train was operated under a negative gauge pressure to prevent outward leaks (except for the 3rd stage scrubber). Dry traps were provided between the reactor and first scrubber and between the first scrubber and second scrubber to prevent back flow of the scrubbing solution. MeSH measurements were performed with an online mass spectrometer as indicated.**

increased the risk of a large MeSH release into the surrounding environment in the event of a system failure or leak during the peak rate period. This off-gassing behavior also required the use of a scrubber system sized to treat a quick release of MeSH at the peak rate period, which would then be under-utilized for the remainder of the reaction. To mitigate the risk associated with running this process at a 45-kg scale, it was desired to run the guanylation reaction under conditions that would distribute the MeSH generation evenly throughout the entire reaction time. In doing so, the wet scrubber system could be sized to treat smaller maximum rates of MeSH generation, potentially increasing its efficiency and utilization.

One strategy for controlling the rate of MeSH generation would be to control the rate of addition of one of the reagents. However, the guanylation reaction was developed as a batch process and additional laboratory work would be required to achieve dose-controlled MeSH generation. A much simpler strategy for MeSH generation control was to change the reaction temperature profile. The kinetic model developed was used to simulate pilot-plant conditions at a 45-kg scale and to predict the MeSH generation rates for different reaction temperature profiles. The following reaction temperature profiles were examined:

1 Heat up to 75 °C over 1 h. Age at 75 °C until reaction completion (kilo laboratory profile).

2 Heat up to 70 °C over 1 h. Age at 70 °C until reaction completion (70 °C).

3 Heat up from 50 to 75 °C following a 5 °C/h temperature ramp. Age at 75 °C until reaction completion (5 °C/h ramp).

4 Heat from 20 to 50 °C over 1 h and age for 1 h, heat up to 60 °C over 1 h and age for 2 h, heat up to 75 °C over 1 h and age until reaction completion (3-step ramp).

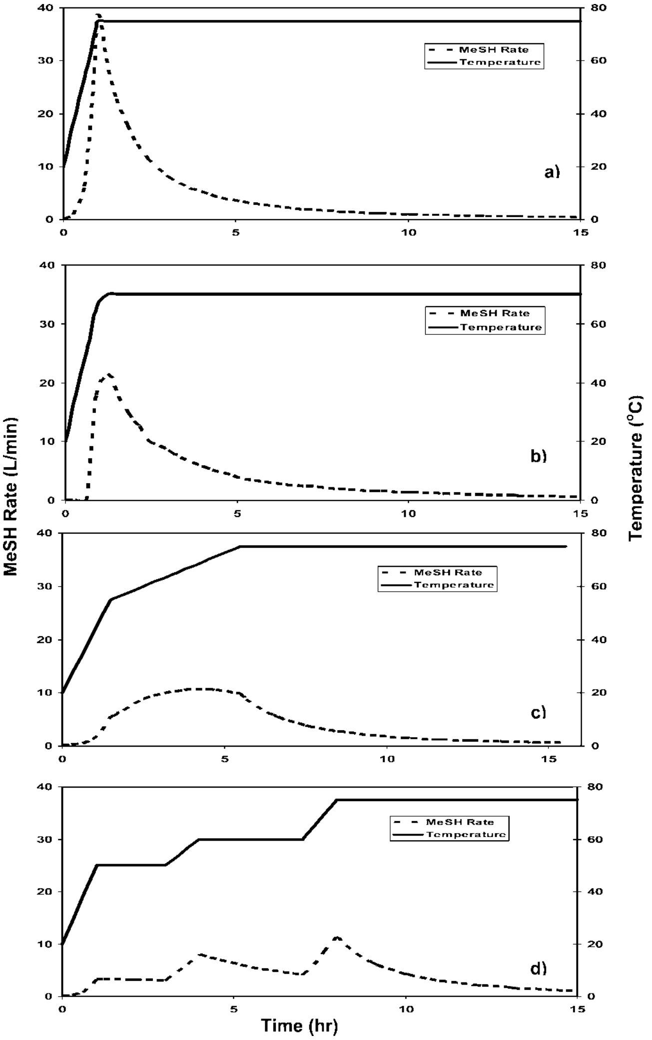

Figure 6. **Model-predicted methanethiol off-gassing profiles for a 45-kg scale: (a) 75 °C, (b) 70 °C, (c) 5 °C/h ramp, and (d) 3-step temperature ramp.**

Figure 6 contains the model-predicted MeSH off-gassing curves for these temperature profiles at a 45-kg batch size. Table 1 compares the different temperature profiles by the predicted maximum off-gassing rate and the time required to reach 95% reaction completion. The kinetic model predicts a maximum MeSH off-gassing rate of 38 L/min when following the 75 °C (kilo laboratory) temperature profile. The maximum off-gassing rate can be reduced to 21 L/min by following the 70 °C

***Table 1.* Model-predicted maximum off-gassing rates and reaction time for 45-kg scale**[a]

temperature profile	maximum MeSH off-gas rate (L/min)	time to 95% conversion (h)
75 °C[b]	38	13
70 °C	21	22
5 °C/h ramp	10	15
3-step ramp	11	16

[a] Performing the guanylation reaction at 70 °C decreases the maximum off-gassing rate by 45% but increases the reaction time by 70%. When a temperature ramp is implemented at the beginning of the reaction, the maximum off-gassing rate is decreased by 73–75% while the reaction time is increased by only 15–23%. [b] Kilo laboratory temperature profile.

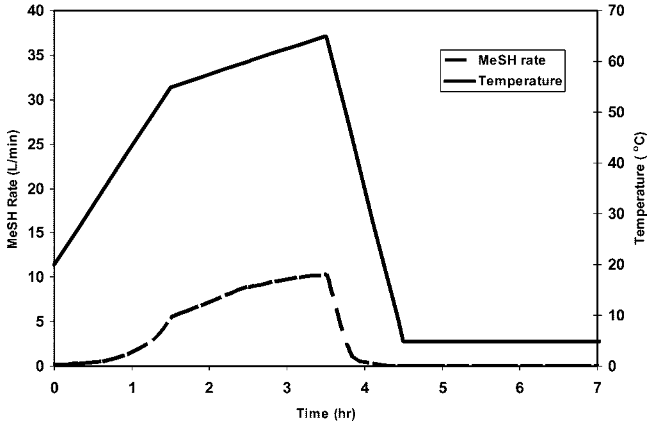

***Figure 7.* Time required for emergency shutdown of the guanylation reaction. The kinetic model predicted that MeSH generation can be halted by applying 1 °C/min cooling. A 70% reduction in the MeSH off-gassing rate is achieved within 10 min and a 95% reduction is achieved within 30 min for a 45-kg batch.**

temperature profile; a 45% reduction. However this profile increases the reaction time from 13 to 22 h; a 70% increase. The kinetic model shows that by implementing a temperature ramp at the beginning of the reaction, the maximum off-gassing rate can be reduced without extensively prolonging the reaction time. Following the 5 °C/h temperature ramp, the maximum off-gassing rate is reduced by 75% to 10 L/min. With this temperature profile 95% reaction completion is achieved within 15 h, an increase of only 15% from the 75 °C (kilo laboratory) temperature profile. Similarly, the maximum off-gassing rate can be reduced to 11 L/min by following the 3-step temperature ramp. The 95% reaction completion mark is reached within 16 h. On the basis of the modeling results, the 5 °C/h and 3-step temperature ramp profiles were selected for implementation in the pilot plant. Laboratory data showed that the alternate temperature profiles identified here had no adverse effect on product quality.

One of the main concerns associated with running the guanylation reaction at scale was the ability to shut down the MeSH generation in the case of an emergency. With a batch process operating in the manner described above, this could only be achieved by rapid cooling of the guanylation reaction mixture. The kinetic model was used to evaluate the ability to shut down the MeSH generation upon rapid cooling. Figure 7 shows the MeSH off-gassing profile when 1 °C/min cooling was applied during the peak off-gas generation period for the 5 °C/h temperature ramp case. A 70% reduction in the MeSH off-gassing rate was achieved within 10 min and, a 95% reduction was achieved within 30 min for a 45-kg batch. Assessment of pilot plant vessel capabilities indicated that 1 °C/min batch cooling could easily be achieved. This analysis showed that the current pilot plant capabilities were adequate to mitigate the risk of a MeSH release during the scale-up of the guanylation reaction and that no additional engineering controls were necessary.

4.3. Design and Efficiency Testing of the Pilot Plant Wet Scrubber. Although the scrubber train utilized in the kilo laboratory provided the desired methanethiol scrubbing efficiency, further scale-up of the scrubber system "as is" was impractical. Vessel limitations of pilot plants and manufacturing sites required a reduction in the redundancy of the scrubber system. Through a combination of the scrubber performance measured in the kilo laboratory and the modeling efforts described above, a wet scrubber consisting of a single, standard, dish bottom pilot plant vessel was proposed (Figure 8). After passing through a dry trap, the methanethiol off-gas would enter the wet scrubber through the standard 2-in. diameter subsurface dip pipe. The liquid level within the scrubber would be such that a liquid height of approximately 85 cm would exist between the bottom of the dip pipe and the liquid surface. Additional scrubbing would be provided within the vapor space of the wet scrubber via recirculation of the scrubbing solution through a fog nozzle installed in the vessel head space.

Prior to pilot-plant implementation of the guanylation reaction, the proposed wet scrubbing system was tested at-scale. A cylinder of methanethiol gas was obtained and connected to the wet scrubber as shown in Figure 9. Using a mass flow meter and a needle valve, methanethiol flow rates ranging from 0.01 to 0.10 kg/min (4.6−46 L/min) were introduced into the scrubber along with nitrogen carrier gas at 50 L/min. Wet scrubber efficiencies were calculated by taking discrete samples from the scrubber vent line for analysis via Draeger-Tubes. As shown in Table 2, all samples indicated that MeSH concentrations in the scrubber vent line were less than the lower detection limit of the Draeger-Tube (<100 ppb). Additionally, this was true for samples taken with and without the scrubber solution recycle loop operational. The calculated efficiency of the wet scrubber under these conditions was >99.9999%.

The pilot plant scrubber test also allowed for verification of the "on-line" methanethiol flow rate determination based on the scrubber energy balance methodology described in section 3.2. Using this model, a good correlation can be seen between the predicted methanethiol flow rates and the discrete methanethiol flow rates measured in the scrubber test (Figure 10).

4.4. Scale-Up Results: Pilot Plant Implementation of the Guanylation Reaction. The efficiency testing on-scale showed that the proposed scrubber system could easily handle the expected MeSH flow rates for the reaction temperature profiles identified via kinetic modeling. The pilot-plant campaign included the execution of three 45-kg guanylation reaction batches. This provided the opportunity to test the performance of the guanylation reaction under both the 5 °C/h and 3-step temperature ramp profiles. Because of the hazards associated with the MeSH generation, minimal sampling was performed

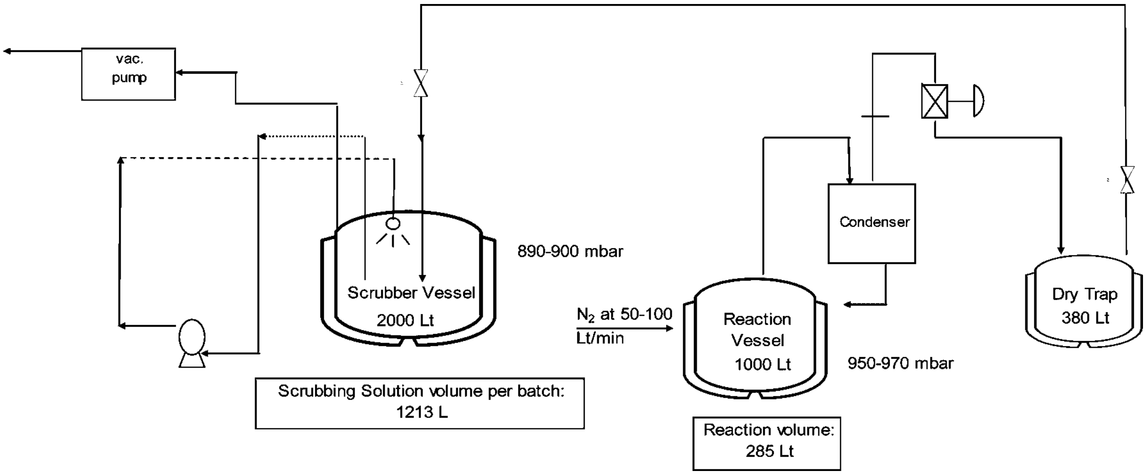

Figure 8. **Pilot plant scrubber setup. The methanethiol off-gas was carried from the reaction vessel through the condenser and dry trap via reduced pressure and introduction of nitrogen carrier gas into the headspace of the reactor. The gas stream then entered the wet scrubber through the standard 2-in. diameter subsurface dip pipe. Additional scrubbing was provided within the vapor space of the wet scrubber via recirculation of the scrubbing solution through a head space fog nozzle.**

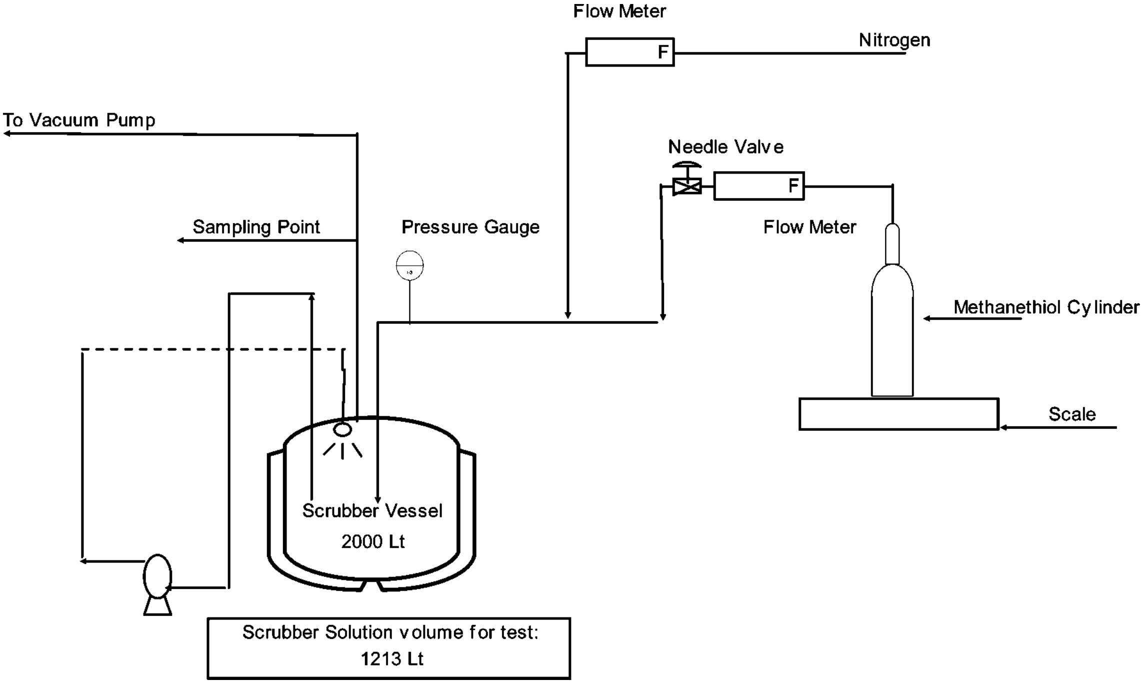

Figure 9. **Pilot plant scrubber test setup. Methanethiol from a pressurized cylinder was fed to the scrubber vessel via a subsurface line at flow rates of 0.01−0.10 kg/min. Nitrogen was used as a carrier gas at 50 L/min. Wet scrubber efficiencies were calculated by taking discrete samples from the scrubber vent line for Draeger-Tube analysis.**

during the guanylation reactions. The guanylation reaction performance was tracked via the energy balance around the scrubber vessel (section 3.2) which yielded the MeSH flow rate to the wet scrubber.

The 5 °C/h temperature profile was implemented during the first and second pilot-plant batches. The batch temperature profile and the observed MeSH flow rate are shown in Figure 11a for the first batch. The batch temperature profile was imported into DynoChem, and the model-predicted MeSH curve was compared to the observed MeSH off-gassing curve. The kinetic model predicted a 9.8 L/min maximum off-gassing rate, and the scrubber energy balance analysis showed that a 9.5 L/min maximum off-gassing rate was achieved. HPLC data showed that 96.5% reaction completion was reached after 21.5 h of reaction time versus the kinetic model predicted 97.7% completion.

Scrubber efficiency measurements were taken via Draeger-Tubes during the first pilot-plant batch. At 6.5 h of reaction time (the peak rate period), the MeSH concentration in the head space of the scrubber vessel was below the Draeger-Tube limit of detection (<100 ppb). This corresponded to a scrubber efficiency >99.9999% and was consistent with the results obtained during the at-scale scrubber efficiency test. The presence of methanethiol was not detected in the operating module or the area surrounding the pilot plant facility. The designed wet scrubber was effective at reducing the concentra-

Table 2. **Scrubber test discrete efficiency measurements**[a]

MeSH flow rate (kg/min)	MeSH scrubber inlet concn (wt %)	MeSH scrubber outlet concn (ppb)	calcd efficiency (%)
0.01	13.8	<100	>99.9999275
0.05	44.4	<100	>99.9999775
0.1	61.5	<100	>99.99998375

[a] Methanethiol flow rates from 0.01 to 0.10 kg/min were introduced into the scrubber along with nitrogen carrier gas at 50 L/min. Wet scrubber efficiencies were calculated by taking discrete samples from the scrubber vent line for Draeger-Tube analysis. MeSH concentrations were less than the Draeger-Tube limit of detection (<100 ppb) for all of the samples taken. The apparent increase in scrubber efficiency at the higher MeSH concentration is due to the limit of detection.

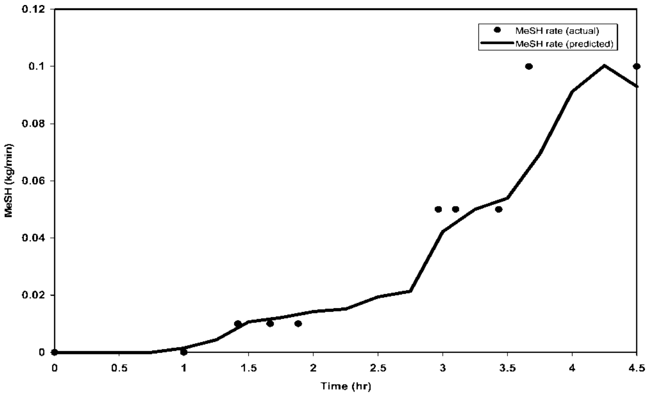

Figure 10. **Actual methanethiol flow rate versus predicted methanethiol flow rate from heat balance. The data gathered during the at-scale scrubber efficiency testing were used to validate the energy balance model for MeSH flow rate determination. The discrete MeSH flow rate measurements were taken with a low flow gas mass meter. This graph shows a good fit between the methanethiol flow rates predicted by the scrubber energy balance and the discrete methanethiol flow rate measurements.**

tion of MeSH to below the OSHA and odor detection limits (10 ppm and 1.6 ppb, respectively). The performance of the second batch following the 5 °C/h temperature profile was consistent with the first batch performance.

The 3-step temperature profile was implemented during the third pilot-plant batch. The temperature profile employed was modified slightly from the profile identified through the kinetic modeling effort. The age at each temperature step was reduced to 1 h, and the final reaction temperature was increased from 75 to 78 °C. These changes were implemented to enhance the guanylation reaction rate. The temperature profile changes increased the maximum off-gassing rate by 20% from that observed during the second pilot plant batch. However, the efficiency measured during the first batch showed that the wet scrubber had enough capacity to handle the increase in maximum MeSH flow rate. The model-predicted and the observed off-gassing profiles are in excellent agreement (Figure 11b). The kinetic model predicts a maximum flow rate of 10 L/min, and the scrubber energy balance shows a peak rate of 11 L/min. HPLC data showed 98% reaction completion after 21.5 h of reaction time compared to the model-predicted 99% conversion.

4.5. Analysis of the Observed Scrubber Efficiency. High scrubbing efficiencies were achieved during the scale-up of the guanylation reaction through the use of a simple, single-stage wet scrubber utilizing sodium hypochlorite as an oxidizing agent. High efficiencies for reduced sulfur compounds have been previously reported for wet scrubbers using chemical oxidation. Kastner and Das observed a methanethiol removal efficiency approaching 100% for a packed bed wet scrubber using ClO_2 as an oxidizing agent.[10] Abe and Machida reported the reduction of methanethiol concentrations to <100 ppb through the use of a packed tower and circulating sodium hypochlorite.[7] Although these reported efficiencies are high, the methanethiol concentrations of the inlet gases were at the parts per million (ppm) level. In this work, the sparged, stirred tank employed as a wet scrubber yielded efficiencies >99.9999% for methanethiol inlet concentrations ranging from 10 to 60 wt%. This work demonstrated the ability to reduce such high methanethiol concentrations to <100 ppb via chemical oxidation in a simple wet scrubber system.

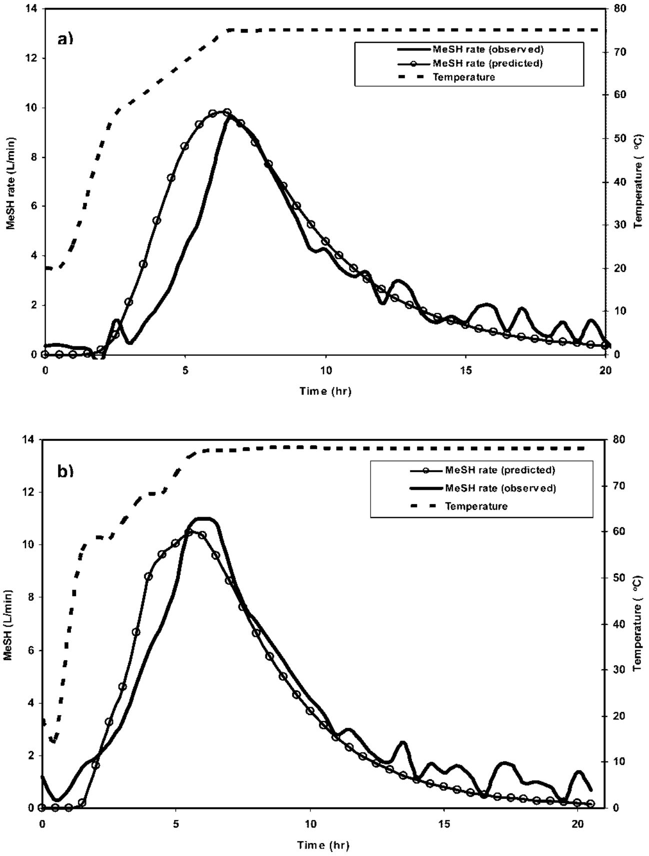

Figure 11. **Pilot-plant results. Model-predicted versus observed off-gassing profiles: (a) first batch following the 5 °C/h temperature ramp and (b) third batch following the modified 3-step temperature profile.**

To explain the high efficiencies observed in this relatively simple scrubber system, CFD simulations were employed to further investigate the transport phenomena and reaction kinetics occurring within the scrubber. Utilizing CFD, the scrubber system was modeled as a methanethiol bubble rising through a stagnant liquid phase containing NaOCl and NaOH. This approach provides a conservative estimation of the bubble's rise distance since the tank mixing effects on the bubble's residence time are ignored (see section 3.3). The expected MeSH bubble

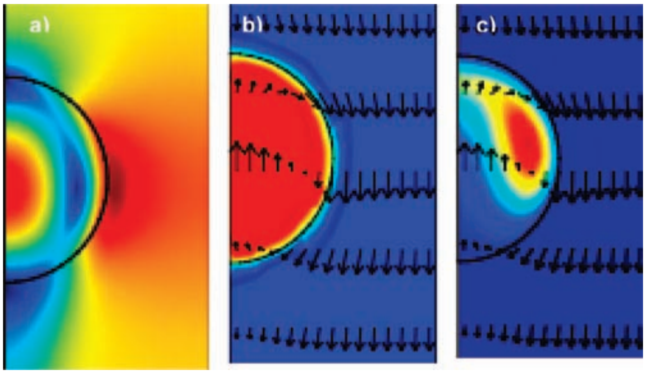

Figure 12. **CFD calculated flow field and concentration profile for a 2-mm methanethiol bubble inside the wet scrubber. (a) Velocity profile at $t = 1$ s. The red color indicates regions of maximum bubble velocity, the blue color indicates minimum velocity regions, and the yellow color indicates median values for the bubble velocity. (b) Flow field and MeSH concentration at $t = 0$ s. The arrows represent the flow field around the bubble, and methanethiol concentration is represented by the color (from greatest as red to least as blue). (c) Flow field and MeSH concentration at $t = 0.04$ s.**

diameters inside the scrubber vessel were determined using Shinnar's correlation.[14] Given the tank impeller diameter and Webber number, this correlation predicted the maximum stable bubble size for a gas in a stirred tank. The velocities around the inlet of the scrubber tank dip pipe were found from CFD flow field calculations (using k-ϵ turbulence models) and were used to calculate the Webber number for the scrubbing system. The diameters of the bubbles investigated were found by using either the impeller diameter or the tank diameter as the characteristic length. From these parameters, the correlation by Shinnar predicted MeSH bubble sizes to be <5 mm inside the scrubbing solution. Given this upper limit, rise distance calculations were performed for bubble diameters of 0.5, 1, 2, and 4 mm as a function of methanethiol removal. The time required to reduce the MeSH concentration by a given percentage was then combined with the bubble's terminal velocity to determine the total distance traveled. Snapshots of the CFD simulations are shown in Figure 12 for a 2-mm bubble. Figure 12a shows the velocity profile of the 2-mm bubble rising within the stagnant scrubbing fluid. Parts b and c of Figure 12 show the flow field as arrows and methanethiol concentration in color for the bubbles at $t = 0$ and 0.04 s, respectively. From these CFD calculations, the methanethiol concentration inside the 2-mm bubble was reduced by greater than 99% in only 0.04 s. As the terminal velocity of the 2 mm bubble was approximately 0.3 m/s, the bubble only traveled 12 mm before 99% of the methanethiol was removed.

This small time-scale for methanethiol removal can be explained by the fast oxidation rate. It has been reported that reactions with rate constants ranging from 4×10^4 to 3×10^8 L/mol s^{-1} achieve rapid removal in wet scrubbers.[15] Kastner et al. reported reaction rates for the oxidation of ethanethiol by $ClO_2 > 4 \times 10^4$ L/mol s^{-1}, a reaction that is chemically similar to the oxidation of methanethiol by NaOCl.[13] The effect of the flow field on the distribution of methanethiol in the bubble can be seen in Figure 12. At regions of high velocity, the methanethiol concentration is low because it is moved away by convection while the concentration remains high at more stagnant regions. Figure 13 shows the rise distance of the bubbles as a function of bubble size for 99%, 99.9%, and 99.99% methanethiol removal. This figure shows that the smaller bubbles (0.5 and 1 mm in diameter) travel relatively short distances to reach the specified level of removal. However, as the bubbles get larger, not only does the travel distance increase with bubble size, but the separation between the 99%, 99.9%, and 99.99% curves also increases. This indicates that increasingly larger levels of liquid height are required for the larger bubbles to achieve the same degree of methanethiol removal as in the case of smaller bubbles.

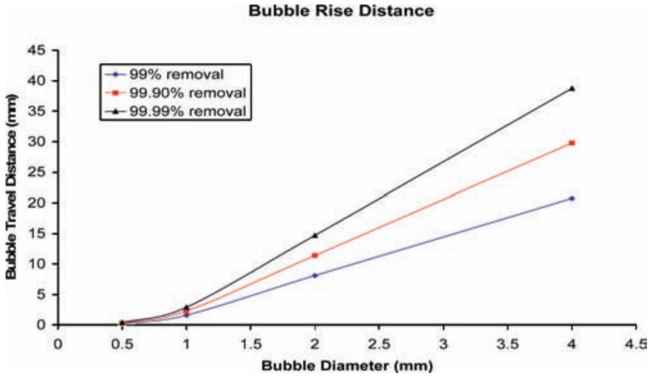

Figure 13. **CFD-calculated rise distance for methanethiol bubbles within the scrubber. For 99.99% removal, the smaller bubbles (0.5 and 1 mm in diameter) travel less than 5 mm, whereas the larger bubbles travel as much as 40 mm. The separation between the 99%, 99.9%, and 99.99% curves increases as the bubble size increases.**

The largest bubble size examined (4 mm) had a rise distance of 40 mm before 99.99% MeSH removal was achieved. During the pilot plant scale-up of the guanylation reaction, the height of the liquid above the dip pipe was 85 cm, a 21-fold excess from the rise distance required for 99.99% MeSH removal from the 4-mm bubble. These calculations showed that if sufficient mixing is ensured (to ensure small bubble sizes), high MeSH scrubbing efficiencies are achievable in the stirred tank setup utilized here.

5. Conclusions

The use of kinetic modeling led to the rapid understanding of the expected MeSH generation rates for a pharmaceutical guanylation reaction at a 45-kg scale. Using the kinetic model, two reaction temperature profiles were identified that reduced the maximum off-gas flow rate by 75% while only increasing the reaction cycle time by 15−23%. The two reaction temperature profiles were verified via laboratory-scale experiments and then successfully implemented at the pilot-plant scale. Addition-

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(14) Lou, H.; Svendsen, H. F. Theoretical model for drop and bubble breakup in turbulent dispersions. *AIChE J.* **1996**, *42*, 1225–1233.

(15) Overcamp, T. J. Modeling oxidizing scrubbers for odor control. *Environ. Sci. Technol.* **1999**, *33*, 155–156.

ally, the reaction kinetics for the pilot-plant batches were tracked by performing an energy balance around the scrubber vessel. This analysis revealed that the developed kinetic model was able to accurately predict MeSH flow rates on-scale.

The ability to reduce MeSH concentrations from 10−60 wt % in the inlet stream to less than 100 ppb in the outlet stream by sodium hypochlorite based chemical oxidation was demonstrated at the pilot-plant scale. The resulting MeSH removal efficiencies of greater than 99.9999% via a simple, stirred tank wet scrubber were further explained by CFD modeling. The mixing characteristics of the scrubber vessel produced small (<5 mm in diameter) MeSH bubbles within the scrubbing solution. As a result of the fast oxidation rate of methanethiol, these small bubbles experienced short rise distances (40 mm) before being completely oxidized. The kinetic and process-modeling-based approach presented here proved effective at quickly identifying and implementing process solutions to mitigate the environmental risk associated with the scale-up of this methanethiol producing reaction.

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